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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/782,590	01/13/1997	SAMUEL ROSE	43/24	9631

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/782,590	ROSE, SAMUEL	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *30 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-82 and 88* is/are pending in the application.

4a) Of the above claim(s) *1-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *69-82 and 88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 30, 2003 has been entered.

2 The Claims 69-82 are pending and currently under examination. Claim 83, canceled in the Paper Submitted January 6, 2003 has been amended, however, no indication of what amendment was intended is found in the claim. In particular there is no underlining or bracketing of words or phrases in the claim. Further, the claim is essentially the same as claim 83, previously rejected and then canceled in the Paper Submitted January 6, 2003. Although Examiner requested clarification of the cancellation of claim 83 in the Paper mailed May 1, 2003, no clarification has been submitted, thus it is clear that Applicant intended to cancel claim 83. However, in the interests of compact prosecution, it will be assumed that Applicant intended to add a new claim drawn to the same limitations as canceled claim 83 and the newly added claim is renumbered under 35 USC 1.126 as claim 88.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Because all claims are drawn to the same invention claimed in parent application Serial No. 08/782, 590, because claim 88 is essentially the same as the previously rejected and then canceled claim 83 wherein said rejection would have been maintained for the reasons of record in the Paper mailed May 1, 2003, and because no additional arguments or amendments to the claims have been

submitted, claims 69-82 remain rejected and newly added claim 88 is rejected for the reasons previously disclosed in the Paper mailed May 1, 2003 as follows:

5. The following rejections are maintained:

Claim Rejections 35 USC 112

6. Claims 69-82 remain rejected and Claim 88 is rejected under 35 USC 112, first paragraph for the reasons previously disclosed in Paper 40, Section 5, pages 2-4.

Applicant argues that (a) the present disclosure provides sufficient disclosure and examples to enable one of skill in the art to make and use these broadly claimed therapeutic agents and points to the general teachings of pages 23-24, (b) Applicant points to Figure 18 wherein the use of a solubilizing polymer coupled to an insoluble compound via a cephalosporanic acid coupling is disclosed, thus the synthesis and radiolabeling of such agents is straightforward organic chemistry and could be achieved using a variety of published methods, (c) biodegradable peptides are known and in the case of the named opio-melanins, these are only partially degradable, (d) Applicant reiterates arguments drawn to dosage information from ADEPT therapy, (e) Applicant states that conversion of a radio-labeled therapeutic agent results in the formation of a radio-labeled extra-cellular precipitate which non-selectively kills all adjacent cells, (f) Applicant points to the Mayers Declaration wherein Dr. Mayers argues that (1) sufficient information is disclosed in the present invention to practice the claimed invention, including methods of making the claimed agents and that in his opinion, the present invention provides sufficient guidance to enable one of skill to prepare and use the broadly claimed first therapeutic agent, (2) the present invention discloses cancer therapy using the claimed therapeutic agent and that killing is induced via the radioactive killing of

the cells adjacent to the radioactivity, that the killing is within the tumor, that the therapeutic agent is generally of low molecular weight so that it is excreted quickly if not transformed to a solid within the tumor, and is only therapeutic when converted to a form that will keep it trapped within the tumor, (3) the radio-labeled precipitate in the extracellular fluid will remain stationary due to the absence of or limited lymphatic draining and the limited number of macrophages within the tumor and Dr. Mayers hypothesizes that the radiolabeled therapeutic agent should be very stable and not undergo much degradation while circulating, (4) Dr. Mayers points to Holt et al, an *in vitro* study in which a precipitate is formed in close proximity to an enzyme that is fixed to a first extracellular precipitate wherein these types of precipitates are used to define exact positions in histological sections, (5) Dr. Mayers argues that the specification describes other types of molecules that can be converted to radioactive precipitates and discloses general teachings drawn to saccharides, cellulose, galactosides and again points to the general teachings on pages 23-24 of the specification, (6) Dr. Mayers teaches the requirements for peptides fit for use in this patent which would provide a radioactive precipitate within the tumor for the requisite 5-10 days and thereby be therapeutic by killing the tumor cells, (7) Dr. Mayers reiterates previous arguments that the well-published literature of ADEPT provides a working example for the present invention and further presents pages of calculations and cites references that are not submitted in order to show that one of ordinary skill in the art would know how to use the claimed invention, (8) Dr. Mayers argues that there are two well defined systems described in the previous literature that would make one skilled in the art predict that the therapeutic agent would form in tumor extracellular space, (A) ADEPT and (B) The *in vitro* work of Holt and others, (9)

the question of inactivating the therapeutic reagent *in vivo* prior to its having its effect is a little difficult to answer since there is no therapeutic effect until it is precipitated in the tumor. Activity from the radio-isotope prior to the formation of the precipitate that occurs in circulation is actually detrimental to the host. Since the pharmacological activity is due to radioacitivty, it can only be deactivated by removing the radio-isotope. The structure has been selected to be stable under physiological conditions, that is the isotope should remain attached to the substrate. Dr. Mayers hypothesizes that any early conversion to a precipitate in normal tissues should expedite the clearance through macrophages present in the normal tissues. Since a large percentage of the injected material is expected to be excreted, the loss of a small amount by early conversion should not hamper this therapeutic approach in any way, (10) Dr. Mayers agrees with Dr. Alan Epstein as drawn to low flow rates in tumors as compared to normal tissues, (11) Dr. Mayers points to the dense packing of tumor cells, thus even in the absence of data one of skill would predict that the precipitate formed in the extracellular space of the tumor will remain trapped between the cells and that the precipitate would be removed very slowly, further, Dr. Mayers points out that tumors lack macrophages, lymphocytes and monocytes and that the precipitate formed in the extracellular space of the tumor would not be removed as quickly as normal tissues. Thus based on the slower flow rates known to occur in tumors, in the absence of macrophages and lymphocytes within the tumor, one of skill could reliably predict that the rate of removal of the precipitate from the tumor would be very much slower from tumor tissue as compared to normal tissue, (g) the conversion of a radio-labeled therapeutic agent results in the formation of a radio-labeled extracellular precipitate and thereby achieves the immobilization of isotopes throughout the

tumor sufficient to kill non-selectively all cells adjacent to the extra-cellular radio-labeled precipitate, (h) regarding the location where the radio-labeled therapeutic agent will be immobilized and the conversion of the radio-labeled therapeutic agent can occur via the action of the bispecific reagent, like ADEPT drugs, the conversion will only occur in the cancer at the site of the bound bispecific reagent, (I) Applicant admits on the record that the extra-cellular precipitate will eventually be removed by phagocytosis or convective flow, but it need remain in the extracellular fluid of the cancer only for a matter of days in order for the present invention to be practiced, (j) Applicant reiterates arguments drawn to tumor flow and discloses that trypan Blue adsorbed to Albumen is retained in tumor tissue for over five days.

The arguments have been considered but have not been found persuasive (a') for the reasons previously set forth, (b') applicant is arguing limitations not recited in the claims as currently constituted, further, it cannot be predicted that the broad construct disclosed in Figure 18 will function as claimed as a therapeutic prodrug for the reasons of record nor is Figure 18 enabling for the broadly claimed invention, (c') for the reasons of record, the invention is not enabled, further, since claim 69 is specifically drawn to opio-melanins which are required by the claim to be non-digestible, it appears that Applicant is admitting on the record that the invention is not enabled (d') the arguments are not persuasive for the reasons of record. Further, Applicant has clearly demonstrated that the instant invention and ADEPT therapy are quite different, thus it could not be expected, nor would it be predictable that the dosage requirements of the two methods would be the same, (e') the argument is not persuasive for the reasons of record. Applicant is invited to submit objective evidence demonstrating the invention functions as claimed,

(f')(1) although it is clear that the agents an be made, it is not clear that the agents can be used so that they will function as contemplated and claimed, as therapeutic agents for the treatment of cancer, Examiner appreciates Dr. Mayers' opinion, however as previously set forth, it is art recognized that the treatment of cancer is an unpredictable art and in the absence of objective evidence in the undeveloped art of the instant invention, it cannot be determined nor could it be predicted that the claimed therapeutic agent will function as contemplated and claimed, (2) Dr. Mayers is arguing limitations not recited in the claims as currently constituted. The specification does not teach that the therapeutic agent is generally of low molecular weight, indeed, claim 72 is specifically drawn to polymers of a molecular weight greater than 1000 daltons. However, Dr. Mayers brings up an important point here in that since the toxic radiolabel will non-selectively kill cells to which it is adjacent, the effects of the radiolabeled therapeutic agent upon the host to which it is administered cannot be predicted if the agent is not of sufficiently small size to be rapidly excreted and it is not clear whether the therapeutic agent could be useful for treating rather than for non-specifically damaging the patient to be treated, (3) Dr. Mayers reiterates arguments drawn to limited lymphatic drainage and number of macrophages within the tumor, the arguments are not persuasive for the reasons of record, Dr. Mayers' hypothesis is also not convincing in the absence of objective evidence. *In vivo* systems are notorious for not doing what they "should" be doing. (4) The Holt reference cannot be evaluated since it was not submitted. However, even if it were to be submitted, the reference as described is clearly not commensurate in scope with the claimed invention which is a therapeutic agent for use *in vivo*, (5) for the reasons of record, the general teachings drawn to soluble and insoluble moieties do not enable the

claimed invention, (6) Dr. Mayers provides teachings of how to determine which peptides that would be useful for the claimed invention, teachings which are not found in the specification as filed. Further Dr. Mayers states that in order to be therapeutic, the radioactive precipitate must be within the tumor for "the requisite 5-10 days" to thereby be therapeutic by killing the tumor cell, Dr. Mayers provides teachings not presented in the specification. There is no mention in the specification as originally filed that the time required for the radiolabeled agent to be in contact with tumor cells is for this period of time, there is no teaching on how to maintain the "precipitate" in the vicinity of the tumor for sufficient time to be therapeutic. In the absence of objective evidence demonstrating that it is possible to maintain the precipitated material for the required time period in order to be therapeutically effective, it cannot be predicted that the claimed therapeutic agent for use as a prodrug will function as claimed, (7) the references have not been considered because they were not submitted, however, even if the references were to be submitted the argument would still not be persuasive for the reasons of record, as clearly stated in Paper No. 15, mailed November 25, 1998 in section 5(b'), the specification clearly states on page 10, paragraph 2 that the "ADEPT approach fails to successfully treat cancer", thus one would not be motivated to, nor would one expect to successfully, use ADEPT as a working example for the claimed invention. Further, it is noted for Applicants convenience that this rejection has been maintained for nearly five years for the reasons of record and although one might make a prediction, the prediction cannot be made with a reasonable expectation of success for the reasons of record, (8) the argument is not persuasive for the reasons set forth previously and above, (9) Dr. Mayers makes it clear that the effects of the "therapeutic" agent are twofold, that is they are

therapeutic after conversion to a precipitate if that precipitate is in the region of the tumor and that they are detrimental, that is anti-therapeutic in circulation and if precipitates are formed in areas not related to the tumor. Dr. Mayers also hypothesizes that a large percentage of the injected material is expected to be excreted and/or converted to precipitate but does not expect this to hamper the therapeutic approach. It is unclear whether the detrimental effects of the agent will outweigh the therapeutic effects, it cannot be determined whether a sufficient quantity of the therapeutic agent will find its way to the tumor to be treated or whether the precipitated product will remain in the appropriate vicinity for the "requisite 5-10 days". The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art. Further, it is not clear what basis is being used for Dr. Mayers' hypotheses. In the absence of objective evidence, it cannot be predicted, nor would it be expected that the "therapeutic agent" for use as a prodrug will function as claimed., (10) the arguments of Dr. Epstein in the Declaration submitted November 16, 1999 were not persuasive for the reasons of record and for the same reasons, the arguments of Dr. Mayers are not persuasive. Further, Dr. Mayers does not mention Dr. Epstein's clear statement that the invention has great potential and can be made and tested. It is clear that, in the absence of objective evidence, Dr. Epstein cannot predict with a reasonable expectation of success that the therapeutic agent will function as claimed, (11) It is clearly well known in the art that tumor cells are densely packed. It is equally well known in the art that tumors are generally impenetrable to antibody sized molecules (solely for Applicant"s information and in response to Dr. Mayers' argument, see WO93/17715, p. 4, attached hereto), thus one would not expect that

the bispecific reagent (which reads on an antibody targeting moiety) required for conversion of the "therapeutic" agent would penetrate the tumor and it would not be expected that the precipitate be trapped between the cells. Although it is well known that flow rates within tumors are slower than within normal tissues, Applicant admits on the record that there are indeed flow rates. It cannot be determined, nor could it be predicted that a sufficient quantity of precipitate, even if formed in the tumor, would remain in the tumor for the "requisite" period disclosed by Dr. Mayers. Given the known density of cells within a tumor. It cannot be predicted how much or if any precipitate could be formed within the tumor or whether the amount formed would function as claimed, that is as a therapeutic for the killing of tumor cells. Examiner reiterates the teachings of the Epstein Declaration, written by one of skill in the art wherein Dr. Epstein states that the invention has great potential and can be made and tested. Patents are not granted for "potential". It is clear that Dr. Epstein states that the potential must be tested. In the absence of objective evidence demonstrating that the invention will function as claimed, the invention is not enabled for the reasons of record, (g') for the reasons set forth above, no one of skill would expect immobilization of isotopes throughout the tumor due to the known dense packing of tumor cells within the tumor and the known fact that tumors are generally impermeant to antibody sized molecules (which would read on the bispecific molecule required to convert the claimed therapeutic agent for use as a prodrug), (h') Dr. Mayers clearly states that a certain amount of conversion will occur in normal tissue at sites other than the tumor (see 3rd from last page of the Mayers Declaration, (I') the specification does not provide guidance on how to keep the precipitate in the extracellular fluid of the cancer for the 5-10 requisite days disclosed by Dr. Mayers

so that it will function as claimed, (j') the arguments are not persuasive for the reasons previously set forth and further, Albumin, a soluble macromolecule, is not commensurate in scope with the precipitates formed from the □therapeutic□ agent used as a prodrug, since, even if they were to be formed in a tumor, these would not be expected to be macromolecules. Applicant's arguments have not been found persuasive and the rejection is maintained. Given that it appears that most, if not all of the arguments submitted have been considered before and that prosecution has continued on this case for five years (suggesting that enough time has occurred for the claimed invention to be made and tested as suggested by Dr. Epstein), Applicant is invited to submit objective evidence demonstrating that the broadly claimed therapeutic agent will function as claimed for consideration After-Final. To be considered, the submitted evidence must be identical in scope with the claimed invention.

New Grounds of Rejection

Claim Rejections 35 USC 112

7. Claims 69-82 are rejected and claim 88 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a radiolabeled prodrug which kills non-selectively all cells adjacent to the extra-cellular radio-labeled precipitate recited in claim 69 and the amendment of claims 75-80 which recite radiolabeled extracellular precipitates have no clear support in the specification and the claims as originally filed. Applicant suggests that there is support for the claimed limitation on pages 23 and 26. The suggested support is not persuasive because a review of page 26 reveals support for an additional therapeutic agent, not that which was originally examined, which is a soluble radioactive toxic agent that is convertible into a

radioactive toxic new form which is capable of remaining in the extra-cellular fluid adjacent to the first extra-cellular precipitate and that the new form of this radioactive toxic substance non-selectively kills all cells adjacent to the first extra-cellular precipitate. The specification does not teach that the soluble radioactive toxic agent in the new form is an insoluble and non-digestible precipitate. It appears that Applicant is attempting to combining both the first and the second therapeutic agents which are contemplated by the specification. Further, a review of page 23 which recites that the first therapeutic agent can be radio-labeled or trace-labeled to be a radioactive therapeutic does not teach or suggest that the radio-agent is a radioactive toxic substance that non-selectively kills all cells adjacent to the first extra-cellular precipitate. The subject matter claimed in claims 69-82 broadens the scope of the invention as originally disclosed in the specification.

8. Claims 69-82 are rejected and claim 88 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of a radiolabeled prodrug for use as a prodrug in claim 69 has no clear support in the specification and the claims as originally filed. Applicant states that at Examiner's suggestion, the new limitation was added to the claims. However, Examiner did not suggest the new limitation in absence of support for the limitation in the specification as filed. Applicant does not point to support for the newly claimed limitation in the specification as originally filed. Although a review of the specification reveals the recitation of □prodrug□ as drawn to ADEPT therapy on p. 9, the prodrug referred to is an inactive drug that is activated upon enzyme conversion. Unlike the ADEPT therapy prodrug, the instant therapeutic agent is not an inactive drug, it is an active radiolabel that kills

cells. In Paper No. 32, pages 14-15, Applicant specifically states that there is no way to make a therapeutically active radio active pro-drug less toxic than the active drug. Thus, since the therapeutic agent now claimed is a radioactive drug that cannot be less active than the active drug, it is not a prodrug in the ADEPT sense and there is no support in the specification for the claims as now constituted. The subject matter claimed in claims 69-82 broadens the scope of the invention as originally disclosed in the specification.

New Grounds of Objection

9. Claim 80 is objected to because the clean copy of the claim and the marked copy of the claim are not the same. It cannot be determined which claim is to be entered. It is noted that claim 80 as disclosed in the marked-up-copy does not make sense. Appropriate correction is required.

10. All other objections and rejections recited in Paper No. 40 are withdrawn.

11. No claims allowed.

12. This is a CPA of Applicant's earlier application S.N. 08/782,590. All claims are drawn to the same invention claimed in the earlier application and, although applicant has filed request for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d), because claim 88 is essentially the same as the previously rejected and then canceled claim 83 wherein said rejection would have been maintained for the reasons of record in the Paper mailed May 1, 2003, and because no Amendment or Response containing either arguments drawn to the instant rejections or amendments to the claims has been submitted, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP ' 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). See M.P.E.P. ' 706.07(b).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvette Eyler, can be reached at 571-272-0871 The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar

Primary Patent Examiner
March 23, 2004